

A single center, open-label trial of isavuconazole prophylaxis against invasive fungal infection in patients undergoing allogeneic hematopoietic stem cell transplant (HCT)

**PROTOCOL FACE PAGE FOR
 MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL**

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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Table of Contents

1.0	PROTOCOL SUMMARY AND/OR SCHEMA	4
2.0	OBJECTIVES AND SCIENTIFIC AIMS	5
3.0	BACKGROUND AND RATIONALE	6
4.0	OVERVIEW OF STUDY DESIGN/INTERVENTION	8
4.1	Design	8
4.2	Intervention	9
5.0	THERAPEUTIC/DIAGNOSTIC AGENTS	10
6.0	CRITERIA FOR SUBJECT ELIGIBILITY	18
6.1	Subject Inclusion Criteria	18
6.2	Subject Exclusion Criteria	18
7.0	RECRUITMENT PLAN	18
8.0	PRETREATMENT EVALUATION	19
9.0	TREATMENT/INTERVENTION PLAN	22
10.0	EVALUATION DURING TREATMENT/INTERVENTION	23
11.0	TOXICITIES/SIDE EFFECTS	24
12.0	CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT	24
13.0	CRITERIA FOR REMOVAL FROM STUDY	25
14.0	BIOSTATISTICS	25
15.0	RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES	26
15.1	Research Participant Registration	26
15.2	Randomization	26
16.0	DATA MANAGEMENT ISSUES	26
16.1	Quality Assurance	27
16.2	Data and Safety Monitoring	27
17.0	PROTECTION OF HUMAN SUBJECTS	28
17.1	Privacy	29
17.2	Serious Adverse Event (SAE) Reporting	29
18.0	INFORMED CONSENT PROCEDURES	30
19.0	REFERENCES	31
20.0	APPENDICES	32

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a single-center, open-label trial. Ninety-two adult patients undergoing first allogeneic hematopoietic stem cell transplantation (HCT) at Memorial Sloan Kettering Cancer Center (MSK) for hematologic malignancies or myeloproliferative disorders will receive isavuconazole (Cresemba) (ISA) as antifungal prophylaxis. Isavuconazole prophylaxis will start on Day (D) +7 (+/-2 days) after stem cell infusion. A window of +/- 2 days is allowed to ensure that recipients of conventional transplants achieve steady levels of calcineurin inhibitors prior to starting isavuconazole. Recipients of T-cell depleted (by CD34+ selection) HCT that do not receive exogenous immunosuppression may start as early as Day +5.

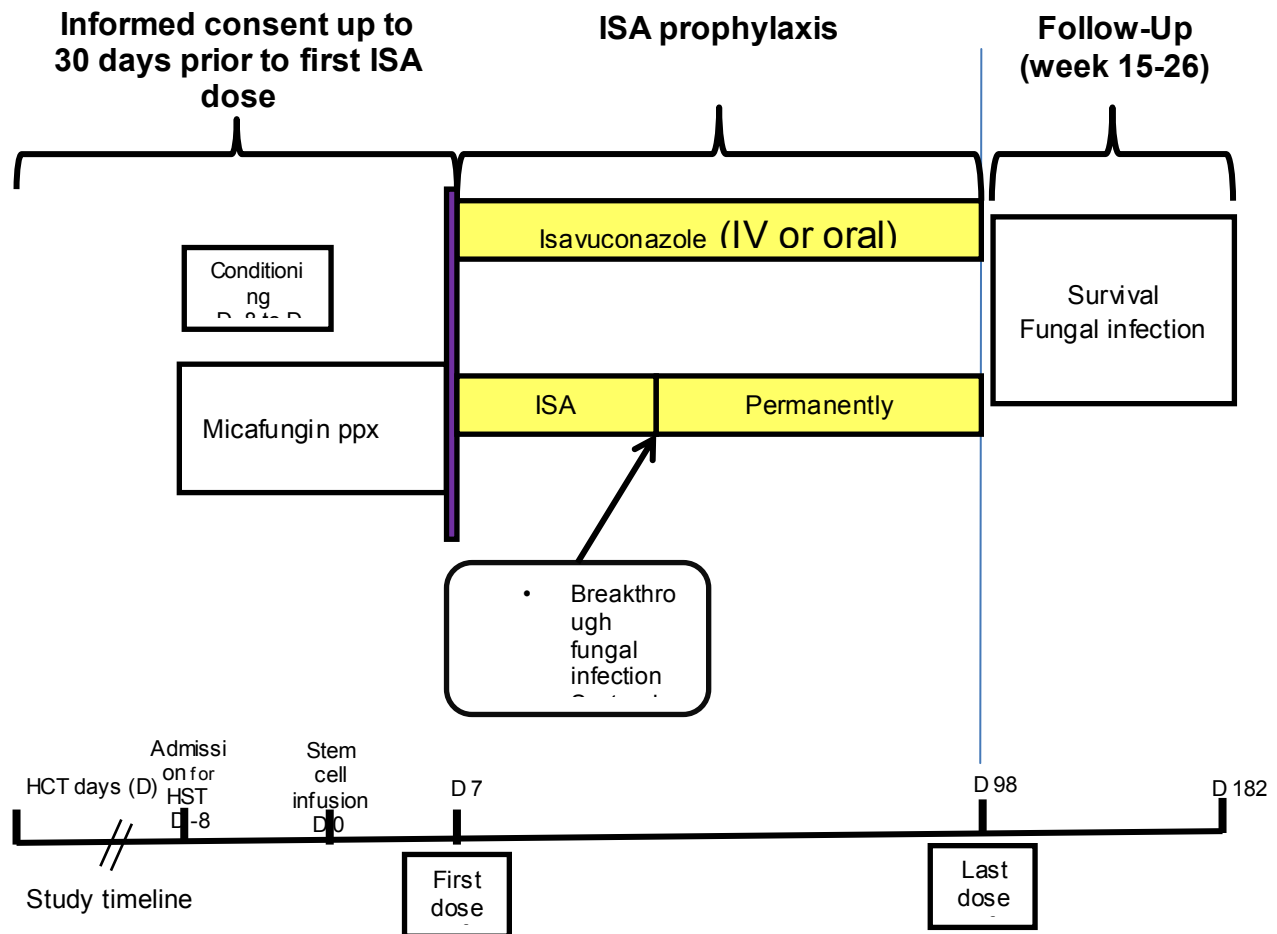
Patients that meet all eligibility criteria but have a contraindication to starting isavuconazole on day +9 may be permitted to start isavuconazole later than day +9 after review and approval by the PI/co-PIs. The reason for starting after day + 9 will be documented in the chart and the CRF.

The maximum duration of isavuconazole prophylaxis will be through D +98 (week 14) post transplant. Patients of conventional peripheral blood or marrow HCT in the absence of graft versus host disease (GVHD) may stop isavuconazole prophylaxis as early as D +60 or between D +60 and D +98 at the discretion of the primary physician. Patients at high risk for invasive mold infection (IMI) including cord blood HCT recipients, and recipients of CD34+ selected HCT, patients with GVHD, CMV infection, and those requiring growth factors to sustain adequate neutrophil count will continue isavuconazole through Day +98.

Patients who develop a suspected or proven fungal infection on isavuconazole prophylaxis, will discontinue isavuconazole and will be treated per standard of care (SOC) at MSK (Appendix 1). If the diagnosis of fungal infection is not confirmed and prophylaxis is interrupted for ≤ 14 days, the patient may resume prophylaxis with isavuconazole. If systemic antifungal therapy is required for >14 days, prophylaxis with isavuconazole will be permanently discontinued.

All patients will be followed through week 26 (day +182) post transplant for survival and occurrence of fungal infection, if applicable. A schema of the study design is shown below:

Figure 1. Schema of study design



Footnote: ^a: A window of +/- 2 days is allowed. ^b: recipients of non cord blood or conventional HCT may stop prophylaxis as early as Day +60 in the absence of GVHD.

Patients that meet all eligibility criteria but have a contraindication to starting isavuconazole on day +9 may be permitted to start isavuconazole later than day +9 after review and approval by the PI/co-PIs. The reason for starting after day + 9 will be documented in the chart and the CRF.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary

- To evaluate the clinical failure rate by week +14 post HCT of isavuconazole prophylaxis per protocol. Clinical failure is defined as:
 - 1) Systemic antifungal therapy for > 14 consecutive days for suspected fungal infection up to week 14.
 - 2) Breakthrough proven or probable fungal infection during the prophylaxis phase. The prophylaxis phase is defined as the period from the first dose of isavuconazole through 7 days after discontinuation (Definitions for proven or probable fungal infections are provided in Appendix 1).
 - 3) Toxicity leading to permanent discontinuation of prophylaxis
 - 4) Adverse event requiring discontinuation.

Secondary

1. Assess serum levels of isavuconazole in patients with grade ≥ 2 acute graft versus host disease (GVHD) of the gastrointestinal tract.
2. Estimate the incidence of probable or proven breakthrough invasive fungal infections (IFIs) with isavuconazole prophylaxis at end of study (week 26).
3. Describe reasons for discontinuation of prophylaxis of isavuconazole. The number and type of adverse events (AE) leading to discontinuation of isavuconazole will be reported. The severity grade and relationship of the AE to isavuconazole will be captured.
4. Estimate overall survival at week 26.

3.0 BACKGROUND AND RATIONALE

HCT is associated with a high risk of invasive fungal infection due to *Candida* and *Aspergillus* species. The risk of infection is associated with the degree and duration of neutropenia, the disruption of protective skin and mucosal surface barriers and the use of corticosteroids. Fluconazole is the only antifungal approved in the USA for chemoprophylaxis during HCT. In the 2 largest trials in HCT, fluconazole prophylaxis was associated with a significant reduction in the frequency of invasive candidiasis compared with placebo in randomized trials. While fluconazole has been widely used as antifungal prophylaxis it does not provide coverage against *Aspergillus*.

Voriconazole, a broad spectrum azole active against *Candida* and *Aspergillus* species, has been increasingly used for antifungal prophylaxis for high risk HCT such as cord blood HCT and *ex vivo* T-cell depleted HCT recipients. In a randomized trial of voriconazole versus fluconazole prophylaxis in standard risk HCT recipients, the overall rates of fungal infections and fungal free survival at 6 and 12 months were similar in the two arms. Notably, there was a significant decrease in infections caused by *Aspergillus* in the voriconazole arm at 6 months.

Voriconazole is extensively metabolized by the liver. Cytochrome CYP2C19, the major enzyme responsible for voriconazole metabolism, exhibits genetic polymorphisms which result in

variability of voriconazole metabolism and exposure. In clinical trials of voriconazole for the treatment of invasive aspergillosis, transaminase elevations were observed in up to 19% of patients with 4% being serious hepatic adverse events. In an observational study of patients with hematologic malignancies, up to 69% of patients developed transaminase elevations. However, only 7% of patients were thought to have clinically significant hepatotoxicity (HT) and required discontinuation of voriconazole.

In a retrospective study from Memorial Sloan Kettering (MSK) of 200 HCT recipients who received voriconazole prophylaxis during 2005-07, 34% developed hepatotoxicity on voriconazole. The median duration of voriconazole administration was 72 days (range: 1–804 days). Biochemical hepatotoxicity occurred in 75% of patients and clinical hepatotoxicity in 25% of patients (Amigues et al. 2010). Voriconazole was discontinued in approximately half of all patients with hepatotoxicity. In a more recent study from MSK, approximately 10% of HCT required alternative antifungal prophylaxis with IV micafungin due to intolerance, toxicity or drug interaction with voriconazole or posaconazole (Neofytos D et al, 2015).

In summary, voriconazole is an attractive agent for prophylaxis because of its broad spectrum covering *Candida* and *Aspergillus* species. However, drug-drug interactions, pharmacokinetic variability, short-term acute toxicities (including photopsia, visual hallucinations, and abnormalities in liver function) and long-term toxicities (such as skin carcinogenesis and fluorosis) concerns about β -cyclodextrin administration in the setting of impaired renal function, and recommendations for therapeutic drug monitoring limit the broad applicability of voriconazole in high risk patients.

Isavuconazonium sulfate (Isavuconazole, Cresemba®) is a broad-spectrum triazole that has demonstrated potent activity in animal models of invasive aspergillosis, mucormycosis and invasive candidiasis. Isavuconazole was approved in 2015 by the US Food and Drug Administration (FDA) for the treatment of invasive aspergillosis and invasive mucormycosis. The water-soluble prodrug isavuconazonium sulfate was developed to facilitate intravenous administration without the need for potentially nephrotoxic excipients such as β -cyclodextrin. Isavuconazole displays excellent bioavailability (roughly 98%) after oral administration without any clinically relevant food effects (Miceli MH et al, 2015).

In a large randomized study of isavuconazole versus voriconazole for treatment of invasive aspergillosis and other filamentous fungi (SECURE), isavuconazole was non inferior to voriconazole in fungal free survival and overall responses. The most important differentiating feature between isavuconazole and voriconazole in the SECURE study was the tolerability and safety profile of isavuconazole, which could allow safer therapy (Maertens JA et al, 2016).

Voriconazole therapy is characterized by a narrow therapeutic window and an established association between elevated concentrations and neurotoxic, hepatic, and visual adverse events. These adverse events, although usually reversible, often lead to premature discontinuation of the drug. Of the drug-related hepatobiliary adverse events reported in the study, 10% were noted in the voriconazole group compared with 2% in the isavuconazole group. Furthermore, key adverse events known to be related to voriconazole (including eye, hepatic, and skin disorders) and discontinuations due to adverse events were significantly less common among isavuconazole treated patients. Given the double-blind nature of the study, this suggests a true difference in the safety features of the two azoles.

There is limited data on the use of isavuconazole as prophylaxis. In an open-label, multi-center dose escalation study of isavuconazole for antifungal prophylaxis in neutropenic patients who had undergone chemotherapy for acute myeloid leukemia (AML) of the 20 twenty subjects who completed the study, 18 were classified as treatment success. The mean plasma of isavuconazole AUC-24 for the dosing period on day 7 were 60.1 ug·h/ml in low-dose cohort and 113.1 ug·h/ml in high-dose cohort. Most of the adverse events were mild-moderate in severity and most common were rash and headache (Cornely OA, 2015). Based on this limited data, the safety and tolerability profile of isavuconazole support isavuconazole prophylaxis in neutropenic patients with AML with 200 mg and 400 mg once-daily maintenance regimens.

We propose a study to evaluate the safety, tolerability and effectiveness of isavuconazole prophylaxis in HCT recipients.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a single center, open-label, single arm study of isavuconazole prophylaxis for the prevention of fungal infections in recipients of allogeneic HCT.

Informed consent will be obtained in the outpatient clinic or during inpatient admission for transplant. Informed consent must be dated ≤ 30 days from first dose of ISA.

Per MSK's standard of care (SOC), HCT recipients receive antifungal prophylaxis with micafungin 150mg IV q24 hours from the day of admission for HCT until Day +7. On Day +7 (+/- 2 days) micafungin will be discontinued and the patient will start isavuconazole prophylaxis. Patients must start isavuconazole prophylaxis between D +5 and D +9.

Patients that meet all eligibility criteria but have a contraindication to starting isavuconazole on day +9 may be permitted to start isavuconazole later than day +9 after review and approval by the PI/co-PIs. The reason for starting after day + 9 will be documented in the chart and the CRF.

Duration of prophylaxis: The duration of prophylaxis will be determined by the patient's risk for fungal infection determined by the treating physician. Recipients of conventional peripheral blood or marrow allografts may stop as early as Day +60 in the absence of GVHD. Patients at high risk for fungal infection including recipients of cord blood HCT, patients with graft versus host disease (GVHD), or with CMV infection, or cytopenic patients requiring growth factor support to sustain adequate neutrophil count, will continue antifungal prophylaxis through Day +98 (week 14) post transplant. The maximum duration of isavuconazole prophylaxis will be through D +98 (week 14). In the event of suspected fungal infection isavuconazole prophylaxis will be held and the patient will receive empiric antifungal therapy per SOC at MSK. If the diagnosis of fungal infection is not confirmed and the patient has received ≤ 14 days of systemic antifungal therapy, isavuconazole prophylaxis may be resumed. If the fungal infection is confirmed or the patient receives more than 14 days of systemic antifungals, isavuconazole prophylaxis will be permanently discontinued.

Interruption of isavuconazole for 14 days or less is permitted for evaluation of possible toxicity. If the toxicity is not deemed to be related to isavuconazole the prophylaxis may be resumed.

Any fungal infection occurring during prophylaxis will be classified according to EORTC/MSG definitions (**Appendix 1**).

Patients will be followed through week 26 post HCT for overall survival, and occurrence of fungal infection.

4.2 Intervention

Intravenous or oral: Isavuconazonium sulfate 372 mg Q 8hour for 6 doses as loading dose, followed by 372 mg Q day as maintenance dose.

Patients who are unable to tolerate oral medications due to mucositis will start isavuconazole intravenously and will have their dose switched to oral formulation when able to tolerate oral medications at the discretion of the clinician. Switching from oral to intravenous formulation of the assigned prophylaxis is acceptable if patients are unable to tolerate oral medication or there is concern for absorption. The bioequivalence has been demonstrated between oral and intravenous formulation. The loading dose is not required when switching between formulations.

The minimum duration of prophylaxis with isavuconazole will be through D +60. Beyond day +60 discontinuation is at the discretion of the treating physician. Patients at high risk for fungal infection such as recipients of cord blood allografts, CD34+ selected allografts, neutropenia requiring growth factors, on immunosuppressants for treatment of GVHD, or other reasons and CMV infection will continue prophylaxis with isavuconazole through day +98. The maximum duration of prophylaxis with isavuconazole on protocol will be through D +98 (week 14). Clinical failure for the primary endpoint is defined in Section 12.0.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Isavuconazole

Overview

Isavuconazonium sulfate (CRESEMBA® **Astellas Pharma US, Inc.** Northbrook, IL) is an azole antifungal indicated for patients 18 years of age and older for use in the treatment of invasive aspergillosis and invasive mucormycosis. Isavuconazonium sulfate is a water soluble prodrug that is rapidly hydrolyzed in blood by esterases to the active moiety, isavuconazole. Isavuconazonium sulfate capsules contain 186 mg of isavuconazonium sulfate (1 capsule) equivalent to 100 mg of isavuconazole. Isavuconazonium sulfate for injection contains 372 mg of isavuconazonium sulfate (1 vial) equivalent to 200 mg of isavuconazole.

Mechanism of Action

Isavuconazole inhibits the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14- α -demethylase. This enzyme is responsible for the conversion of lanosterol to ergosterol. An accumulation of methylated sterol precursors and a depletion of ergosterol within the fungal cell membrane weakens the membrane structure and function.

Activity in vitro and in clinical infections

Isavuconazole has activity against most strains of the following microorganisms, both in vitro and in clinical infections: *Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus niger*, and Mucorales such as *Rhizopus oryzae* and *Mucormycetes* species.

In vitro and animal studies suggest cross-resistance between isavuconazole and other azoles. The relevance of cross-resistance to clinical outcome has not been fully characterized.

General Pharmacokinetics

In healthy subjects, the pharmacokinetics of isavuconazole following oral administration of CRESEMBA capsules at isavuconazole equivalent doses up to 600 mg per day (6 capsules) are dose proportional (Table 1). Based on a population pharmacokinetics analysis of healthy subjects and patients, the mean plasma half-life of isavuconazole was 130 hours and the mean volume of distribution (V_{ss}) was approximately 450 L following intravenous administration.

Table 1. Steady State Pharmacokinetic Parameters of Isavuconazole Following Administration of Isavuconazole (CRESEMBA) Capsules

Parameter	CRESEMBA 2 Capsules ^a (n = 37)	CRESEMBA 6 Capsules ^a (n = 32)
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C_{max} (ng/mL)		
Mean SD CV %	7499 1893.3 25.2	20028 3584.3 17.9
t_{max} (h)		
Median	3.000	4.000
Range	2.0 – 4.0	2.0 – 4.0
AUC (h•ng/mL)		
Mean SD CV %	121402 35768.8 29.5	352805 72018.5 20.4

^a Each capsule contains the equivalent of 100 mg of isavuconazole.

Absorption

After oral administration of isavuconazole in healthy volunteers, the active moiety, isavuconazole, generally reaches maximum plasma concentrations (C_{max}) 2 hours to 3 hours after single and multiple dosing. The absolute bioavailability of isavuconazole following oral administration of CRESEMBA is 98%. No significant concentrations of the prodrug or inactive cleavage product were seen in plasma after oral administration. Following intravenous administration of CRESEMBA, maximal plasma concentrations of the prodrug and inactive cleavage product were detectable during infusion and declined rapidly following the end of administration. The prodrug was below the level of detection by 1.25 hours after the start of a 1 hour infusion. The total exposure of the prodrug based on AUC was less than 1% that of isavuconazole. The inactive cleavage product was quantifiable in some subjects up to 8 hours after the start of infusion. The total exposure of inactive cleavage product based on AUC was approximately 1.3% that of isavuconazole.

Effect of Food

Coadministration of CRESEMBA equivalent to isavuconazole 400 mg oral dose with a high-fat meal reduced isavuconazole C_{max} by 9% and increased AUC by 9%. CRESEMBA can be taken with or without food.

Distribution

Isavuconazole is extensively distributed with a mean steady state volume of distribution (V_{ss}) of approximately 450 L. Isavuconazole is highly protein bound (greater than 99%), predominantly to albumin.

Metabolism

In vitro studies show that isavuconazonium sulfate is rapidly hydrolyzed in blood to isavuconazole by esterases, predominately by butylcholinesterase. Isavuconazole is a

substrate of cytochrome P450 enzymes 3A4 and 3A5. Following single doses of [cyano 14C] isavuconazonium and [pyridinylmethyl 14C] isavuconazonium in humans, in addition to the active moiety (isavuconazole) and the inactive cleavage product, a number of minor metabolites were identified. Except for the active moiety isavuconazole, no individual metabolite was observed with an AUC greater than 10% of drug related material. In vivo studies indicate that CYP3A4, CYP3A5 and subsequently uridine diphosphate-glucuronosyltransferases (UGT) are involved in the metabolism of isavuconazole.

Excretion

Following oral administration of radio-labeled isavuconazonium sulfate to healthy volunteers, a mean of 46.1% of the total radioactive dose was recovered in the feces and 45.5% was recovered in the urine.

Renal excretion of isavuconazole itself was less than 1% of the dose administered. The inactive cleavage product is primarily eliminated by metabolism and subsequent renal excretion of the metabolites.

Renal elimination of intact cleavage product was less than 1% of the total dose administered. Following intravenous administration of radio-labeled cleavage product, 95% of the total radioactive dose was excreted in the urine.

Special populations

Renal Impairment

Total isavuconazole AUC and C_{max} were not affected to a clinically meaningful extent in subjects with mild, moderate and severe renal impairment relative to healthy controls. No dose adjustment is necessary in patients with renal impairment. Isavuconazole is not readily dialyzable. A dose adjustment is not warranted in patients with ESRD.

Hepatic Impairment

After a single dose of CRESEMBA equivalent to 100 mg of isavuconazole was administered to 32 patients with mild (Child-Pugh Class A) hepatic impairment and 32 patients with moderate (Child-Pugh Class B) hepatic impairment (16 intravenous and 16 oral patients per Child-Pugh Class), the least squares mean systemic exposure (AUC) increased 64% and 84% in the Child-Pugh Class A group and the Child-Pugh Class B group, respectively, relative to 32 age and weight-matched healthy subjects with normal hepatic function. Mean C_{max} was 2% lower in the Child-Pugh Class A group and 30% lower in the Child-Pugh Class B group. The population pharmacokinetic evaluation of isavuconazole in healthy subjects and patients with mild and moderate hepatic impairment demonstrated that the mild and moderate hepatic impairment population had 40% and 48% lower isavuconazole clearance (CL) values, respectively, compared to the healthy population. It is recommended that the standard CRESEMBA loading dose and maintenance dose regimen be utilized in patients with mild to moderate hepatic disease.

CRESEMBA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

Pharmacokinetic/Pharmacodynamic Relationship

In patients treated with CRESEMBA for invasive aspergillosis in a controlled trial, there was no significant association between plasma AUC or plasma isavuconazole concentration and efficacy.

Cardiac Electrophysiology

The effect on QTc interval of multiple doses of CRESEMBA capsules was evaluated. CRESEMBA was administered as 2 capsules (equivalent to 200 mg isavuconazole) three times daily on days 1 and 2 followed by either 2 capsules or 6 capsules (equivalent to 600 mg isavuconazole) once daily for 13 days in a randomized, placebo- and active-controlled (moxifloxacin 400 mg single dose), four-treatment-arm, parallel study in 160 healthy subjects.

Isavuconazole resulted in dose-related shortening of the QTc interval. For the 2-capsule dosing regimen, the least squares mean (LSM) difference from placebo was -13.1 msec at 2 hours postdose [90% CI: -17.1, -9.1 msec]. Increasing the dose to 6 capsules resulted in an LSM difference from placebo of -24.6 msec at 2 hours postdose [90% CI: -28.7, -20.4].

CRESEMBA was not evaluated in combination with other drugs that reduce the QTc interval, so the additive effects are not known.

Table 2. Dosage Regimen for CRESEMBA

	Loading Dose	Maintenance Dose ^c
CRESEMBA for Injection 372 mg ^a of isavuconazonium sulfate per vial	1 reconstituted vial (372 mg ^a) intravenously every 8 hours for 6 doses (48 hours)	1 reconstituted vial (372 mg ^a) intravenously once daily
CRESEMBA Capsules 186 mg ^b of isavuconazonium sulfate per capsule	2 capsules (372 mg ^a) orally every 8 hours for 6 doses (48 hours)	2 capsules (372 mg ^a) orally once daily

^a 372 mg of isavuconazonium sulfate is equivalent to 200 mg of isavuconazole ^b 186 mg of isavuconazonium sulfate is equivalent to 100 mg of isavuconazole ^c Start maintenance doses 12 to 24 hours after the last loading dose

Adverse Drug Reactions

The most frequent adverse reactions observed in the pivotal trial of isavuconazole compared to voriconazole were nausea, vomiting, diarrhea, headache, elevated liver chemistry tests, hypokalemia, constipation, dyspnea, cough, peripheral edema, and back pain (refer to supplemental table for treatment-emerging adverse events occurring in $\geq 5\%$ of population in the Pivotal study by Maertens JA et al).

Table 3 shows a comparison of treatment emerging adverse effects in the isavuconazole and voriconazole arms from the pivotal trial of isavuconazole versus voriconazole for the treatment of invasive aspergillosis (Maertens JA et al).

The most important differentiating feature between isavuconazole and voriconazole was the tolerability and safety profile of isavuconazole, which could allow safer therapy. Voriconazole therapy is characterized by a narrow therapeutic window and an established association between elevated concentrations and neurotoxic, hepatic, and visual adverse events. These adverse events, although usually reversible, often lead to premature discontinuation of the drug. Of the drug-related hepatobiliary adverse events reported in the pivotal study, 26 (10%) were noted in the voriconazole group compared with five (2%) in the isavuconazole group. In the same study, key adverse events known to be related to voriconazole (including eye, hepatic, and skin disorders) and discontinuations due to adverse events were significantly less common among isavuconazole-treated patients. Given the double-blind nature of the study, this suggests a true difference in the safety features of the two azoles. Whether the higher proportion of adverse events with voriconazole was due to supratherapeutic drug exposure of isavuconazole cannot be excluded without therapeutic drug monitoring; however, the effect of therapeutic drug monitoring on the incidence of these adverse events remains speculative.

Table 3: Treatment-emergent adverse events by system organ class

	Isavuconazole (n=257)	Voriconazole (n=259)	p value
Overall	247 (96%)	255 (98%)	0.122
Gastrointestinal disorders	174 (68%)	180 (69%)	0.705
Infections and infestations	152 (59%)	158 (61%)	0.719
General disorders and administrative site conditions	148 (58%)	144 (56%)	0.658
Respiratory, thoracic, and mediastinal disorders	143 (56%)	147 (57%)	0.859
Metabolism and nutrition disorders	108 (42%)	121 (47%)	0.289
Nervous system disorders	95 (37%)	89 (34%)	0.582
Skin and subcutaneous tissue disorders *	86 (33%)	110 (42%)	0.037 [†]
Investigations (abnormal laboratory tests)	85 (33%)	96 (37%)	0.357
Blood and lymphatic system disorders	77 (30%)	82 (32%)	0.703

	Isavuconazole (n=257)	Voriconazole (n=259)	p value
Psychiatric disorders[†]	70 (27%)	86 (33%)	0.151
Musculoskeletal and connective tissue disorders	69 (27%)	77 (30%)	0.495
Vascular disorders	67 (26%)	77 (30%)	0.378
Renal and urinary disorders	55 (21%)	58 (22%)	0.832
Cardiac disorders	43 (17%)	57 (22%)	0.148
Eye disorders[‡]	39 (15%)	69 (27%)	0.002 [¶]
Injury, poisoning, and procedural complications	33 (13%)	39 (15%)	0.526
Hepatobiliary disorders[§]	23 (9%)	42 (16%)	0.016 [¶]
Immune system disorders	20 (8%)	25 (10%)	0.533
Neoplasms benign, malignant and unspecified	19 (7%)	31 (12%)	0.101
Ear and labyrinth disorders	14 (5%)	13 (5%)	0.846
Reproductive system and breast disorders	8 (3%)	13 (5%)	0.373
Endocrine disorders	5 (2%)	3 (1%)	0.503
Congenital, familial, and genetic disorders	3 (1%)	2 (1%)	0.685
Social circumstances	0	1 (<1%)	>0.999

Coded in MedDRA 12.1. Adverse events (preferred terms) reported in safety population (all patients who received first dose of study drug).

*Rash, 17/257 (7%) vs 28/259 (11%); erythema, 9/257 (4%) vs 15/259 (6%); skin lesion, 4/257 (2%) vs 8/259 (3%); and drug eruption, 3/257 (1%) vs 11/259 (4%).

†Hallucinations, 6/257 (2%) vs 11/259 (4%); visual hallucinations, 3/257 (1%) vs 11/259 (4%); and agitation, 2/257 (1%) vs 7/259 (3%).

‡Visual impairment, 4/257 (2%) vs 19/259 (7%); photophobia, 2/257 (1%) vs 6/259 (2%); reduced visual acuity, 1/257 (<1%) vs 6/259 (2%); and retinal haemorrhage 0/257 (0%) vs 5/259 (2%).

§Hyperbilirubinaemia, 5/257 (2%) vs 10/259 (4%); abnormal hepatic function, 4/257 (2%) vs 9/259 (3%); jaundice, 1/257 (<1%) vs 6/259 (2%); and cholestasis, 1/257 (<1%) vs 6/259 (2%).

¶Statistical significance at $p \leq 0.05$ (Fisher's exact test).

The safety and pharmacokinetics of Isavuconazole as antifungal prophylaxis in acute myeloid leukemia patients with neutropenia was evaluated in a Phase 2, Dose Escalation Study (Cornely OA et al). In this small study comprising of a total of 23 patients, 12 patients were allocated to the “high dose” arm, which is equivalent of the currently approved dose of isavuconazole. A total of 77 TEAEs were reported for 10 (90.9%) patients in the low-dose cohort compared with

120 TEAEs in 12 (100%) patients in the high-dose cohort. The most commonly reported TEAEs were fever ($n = 6$ [54.5%]), diarrhea ($n = 4$ [36.4%]), and rash ($n = 4$ [36.4%]) in the low-dose cohort, compared with fever ($n = 12$ [100%]) and nausea ($n = 8$ [66.7%]) in the high-dose cohort. The majority of the TEAEs reported in both cohorts were of mild-to-moderate intensity ([Table 4](#)). One SAE was reported, a case of life-threatening respiratory distress in a patient in the high-dose cohort, which was not considered to be attributable to the study medication.

TABLE 4 Treatment-emergent AEs and drug-related TEAEs by severity grade^a

TEAE characteristics by type	No. (%) by severity in:					
	Low-dose cohort ($n = 11$) ^b			High-dose cohort ($n = 12$) ^c		
	Mild	Moderate	Severe	Mild	Moderate	Severe
All TEAEs						
Total no.	45	28	4	45	49	25
Most commonly reported ^d						
Fever	3 (27.3)	1 (9.1)	2 (18.2)	2 (16.7)	6 (50.0)	4 (33.3)
Diarrhea	3 (27.3)	1 (9.1)	0 (0)	4 (33.3)	2 (16.7)	0 (0)
Rash	1 (9.1)	3 (27.3)	0 (0)	2 (16.7)	1 (8.3)	1 (8.3)
Cough	1 (9.1)	2 (18.2)	0 (0)	3 (25.0)	1 (8.3)	1 (8.3)
Nausea	0 (0)	1 (9.1)	0 (0)	4 (33.3)	2 (16.7)	2 (16.7)
Thrombocytopenia	0 (0)	0 (0)	0 (0)	0 (0)	1 (8.3)	3 (25.0)
Drug-related						
Total no.	6	3	2	9	8	4
Most commonly reported ^e						
Hypotension	2 (18.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Vertigo	2 (18.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Headache	0 (0)	1 (9.1)	0 (0)	1 (8.3)	1 (8.3)	0 (0)
Rash	1 (9.1)	0 (0)	0 (0)	1 (8.3)	1 (8.3)	0 (0)
Cough	0 (0)	0 (0)	0 (0)	2 (16.7)	0 (0)	0 (0)

^a Safety population (received 2:1 dose of study medication); AE severity defined by the Common Terminology Criteria for Adverse Events guidelines. TEAE, treatment-emergent adverse event.

^b Isavuconazole administered as a 200-mg once-daily maintenance regimen; no life-threatening TEAEs were reported in this cohort.

^c Isavuconazole administered as a 400-mg once-daily maintenance regimen; a single life-threatening TEAE of respiratory distress that was not drug related was reported in this cohort.

^d TEAEs were reported by >30% of patients in either cohort; each AE was counted only once at its most extreme severity in each patient.

^e TEAEs were reported by 2:2 patients in either cohort.

Hepatic

Hepatic adverse drug reactions (e.g., elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin) have been reported in clinical trials. The elevations in liver-related laboratory tests were generally reversible and did not require discontinuation of CRESEMBA. Cases of more severe hepatic adverse drug reactions including hepatitis, cholestasis or hepatic failure including death have been reported in patients with serious underlying medical conditions (e.g., hematologic malignancy) during treatment with azole antifungal agents, including CRESEMBA.

Evaluate liver-related laboratory tests at the start and during the course of CRESEMBA therapy. Monitor patients who develop abnormal liver-related laboratory tests during CRESEMBA

therapy for the development of more severe hepatic injury. Discontinue CRESEMBA if clinical signs and symptoms consistent with liver disease develop that may be attributable to CRESEMBA

Infusion-Related Reactions

Infusion-related reactions including hypotension, dyspnea, chills, dizziness, paresthesia, and hypoesthesia were reported during intravenous administration of CRESEMBA. Discontinue the infusion if these reactions occur

Hypersensitivity Reactions

Serious hypersensitivity and severe skin reactions, such as anaphylaxis or Stevens Johnson syndrome, have been reported during treatment with other azole antifungal agents. Discontinue CRESEMBA if a patient develops a severe cutaneous adverse reaction. There is no information regarding cross-sensitivity between CRESEMBA and other azole antifungal agents. Caution should be used when prescribing CRESEMBA to patients with hypersensitivity to other azoles.

Drug Interactions

Coadministration of CRESEMBA with strong CYP3A4 inhibitors such as ketoconazole or high-dose ritonavir and strong CYP3A4 inducers such as rifampin, carbamazepine, St. John's wort, or long acting barbiturates is contraindicated. A list of CYP3A4 inducers is listed in Appendix 2. Under drugs that concentration is affected by voriconazole.

The most common CYP3A4 Inhibitors used in HCT recipients include the immunosuppressants Sirolimus, Cyclosporine and Tacrolimus. In the Lexicomp the degree of interaction of isavuconazole for these immunosuppressants is C: "monitor therapy". (<http://online.lexi.com/lco/action/interact>).

Other C3A4 inhibitors that may be used in HCT recipients include Benzodiazepines, HMG-CoA Reductase Inhibitors (Statins), Dihydropyridine Calcium Channel Blockers, Oral Contraceptives containing ethinyl estradiol and norethindrone, Omeprazole, Methadone, Fentanyl and Oxycodone. The degree of interaction of isavuconazole with the above listed medications is variable. Alternatives are available where modification of therapy is recommended.

Formulation and labeling

Capsules

CRESEMBA (isavuconazonium sulfate) capsules are available in aluminum blister packs. Each capsule contains 186 mg isavuconazonium sulfate (equivalent to 100 mg of isavuconazole). Capsules are opaque and elongated, and have a Swedish orange (reddish-brown) body imprinted with the Astellas logo in black ink and a white cap imprinted with "766" in black ink. Store in original container to protect from moisture. Capsules are packaged in aluminum blister packs, seven (7) capsules per sheet with desiccant.

Injection

CRESEMBA (isavuconazonium sulfate) for injection is supplied in a single-dose vial as white to yellow sterile lyophilized powder containing 372 mg isavuconazonium sulfate (equivalent to 200 mg isavuconazole).

Storage requirements

Store CRESEMBA capsules at 20°C to 25°C (68°F to 77°F) in the original packaging to protect from moisture. Excursions are permitted from 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

Store CRESEMBA for injection un-reconstituted vials at 2° to 8°C (36° to 46°F) in a refrigerator. CRESEMBA is a single dose vial of unpreserved sterile lyophile. Following reconstitution of the lyophile with water for injection USP, the reconstituted solution should be used immediately, or stored below 25°C for a maximum of 1 hour prior to preparation of the patient infusion solution. The prepared infusion solution should be kept for not more than 6 hours at room temperature [20°C to 25°C (68°F to 77°F)] or 24 hours at 2° to 8°C (36° to 46°F) prior to use. CRESEMBA for injection vials are for single-dose use only

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

1. Subjects of greater than or equal to 18 years of age of either sex and of any race.
2. Have received first peripheral blood, marrow or cord blood transplant from a family or unrelated donor for hematologic malignancy or myeloproliferative disorder.

6.2 Subject Exclusion Criteria

1. Proven or probable aspergillosis or other mold infection or deep mycoses including hepatosplenic candidiasis less than 60 days from first dose of ISA.
2. History of allergy or intolerance to ISA.
3. Clinically significant elevation of liver function tests prior to the first day of dosing (FDD) that at the discretion of the treating physician would preclude the administration of an azole antifungal.
4. Familial short QT syndrome.

7.0 RECRUITMENT PLAN

Candidates for the study will be identified at the BMT service weekly scheduling meeting.

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

Approximately 12 patients per month are admitted for allogeneic HCT. We estimate to accrue approximately 4 patients per month to complete accrual of 100 subjects in 24 months and follow up by 36 months.

All eligible patients will be approached for participation in the study. Patients will not be paid for participation in the study. All visits for the study will occur during visits for routine clinical care.

No travel reimbursement will be provided for study visits.

8.0 PRETREATMENT EVALUATION

The assessments below are conducted as part of routine care during admission for HCT.

- History and physical examination including vital signs performed on the day of first dose of isavuconazole.
- Baseline CT chest per MSK guidelines within 60 days from first dose of ISA.
- Baseline EKG obtained within 30 days from first dose of ISA

The following baseline blood tests will be collected on the day of the first dose of ISA and are part of routine care.

- Hematology: complete blood count and platelet counts.

The following baseline blood tests will be collected within 48 hours of the first dose of ISA and are part of routine care:

- Serum chemistry: creatinine, blood urea nitrogen, AST, ALT, alkaline phosphatase, total bilirubin, albumin, electrolytes.

A table of study procedures and assessments is provided below (Table 5).

Table 5. STUDY PROCEDURES:

	Up to 30 days prior to FDD		Prophylaxis period			Follow up	
Transplant Week		Day 7(+/-2)	Week 2-4	Week 5-7	Week 8-14	Week 15	Week 16-26
Study Week		Day 1 / FDD	Week 1-3 biweekly	Week 4-7 weekly	Week 8-14 Once every 2 weeks	Week 15 (or ISA termination +7days)	Week 16-26 Every 4 weeks
<i>visit windows</i>			±1 day	± 3days	± 5days	+ 3 days	±7 days
Informed consent	x						
History		x		x	x		
Physical exam		x					
Antifungal Medication Assessment			x	x	x	x	x
Interim history ^a			x	x	x	x	x
Directed exam ^a			x	x	x	x	
Vital signs		x	x	x	x	x	
Hematology ^b		x	x	x	x	x	
Chemistry ^c		x	x	x	x	x	
Serum isavuconazole concentration ^c		← x →					
Microbiology ^f		← x →					
First Dose of ISA (FDD)		x					
SAE assessment ^g		x	x	x	x ^g	x	
Study drug termination					x ^h		

^a Directed physical exam should focus on all organ systems clinically relevant in the setting of invasive fungal infections

^b Complete blood count and platelet count

^c Electrolytes creatinine, glucose, urea nitrogen, alkaline phosphatase, AST, ALT, albumin, total bilirubin. These must be done within 48 hours of the first dose.

^e Serum isavuconazole level will be performed once when patients have been on a steady oral dose of isavuconazole for 10-14 days, at the discretion of the investigator.

In addition, patients who develop GI GVHD grade 2 or higher may have additional levels of isavuconazole at, but not limited to, the following time points: diagnosis of GVHD, after 2 weeks of treatment for GVHD, and resolution of GVHD symptoms, at the discretion of the investigator. Additional samples may be collected at the discretion of the investigator.

Patients who develop breakthrough fungal infections on isavuconazole prophylaxis will have an isavuconazole level at the time of discontinuation of isavuconazole.

^f Diagnostic studies will be performed per standard of care if a patient develops suspected fungal infection. Work up may include Serum fungal markers (galactomannan, BD g lucan) bronchoscopy or tissue sampling of infected sites for microbiologic studies and histopathologic examination.

^g SAE occurring up to 30 days after termination of isavuconazole will be reported (section 17,2).

^h If patient discontinues ISA prophylaxis prior to week 14, the post treatment schedule will be followed. End of treatment assessment to be conducted when the patient permanently discontinues ISA prophylaxis.

9.0 TREATMENT/INTERVENTION PLAN

After signing informed consent patients will be registered by the Office of Clinical Research Protocol Participant Registration (CRPPR) through the Clinical Research Database.

Per MSK SOC patients will receive micafungin 150mg intravenously every 24 hours starting on the day of admission for HCT. Micafungin will be diluted in 100 ml of 0.9% Sodium Chloride. The solution will be kept at room temperature and protected from light. The entire infusion solution will be infused over 1 hour within 24 hours of reconstitution. The tubing will get flushed at the end of the infusion to secure the entire dose of drug was infused.

Isavuconazole (isavuconazonium sulfate) 372 mg Q8hr for 6 doses as loading dose, followed by 372 mg QD as maintenance dose will start as described on Day +7 (+/-2 days). Isavuconazole may be administered intravenously until patients are able to receive oral medications at the discretion of the treating physician.

Patients that meet all eligibility criteria but have a contraindication to starting isavuconazole on day +9 may be permitted to start isavuconazole later than day +9 after review and approval by the PI/co-PIs. The reason for starting after day + 9 will be documented in the chart and the CRF.

If the patient develops clinically suspected or documented fungal infection isavuconazole will be discontinued and the patient will start antifungal therapy per SOC. Work up to establish diagnosis of fungal infection will be done by the treating physician as indicated. If the diagnosis of fungal infection is not confirmed and ISA has been interrupted for ≤ 14 days, patients may resume ISA prophylaxis.

During admission for transplant the patients will be monitored as inpatients. After discharge the patients will be monitored at the outpatients BMT clinic at least weekly through d +60, once every 2 weeks through d +98 and once at least every 4 weeks through week 26. Blood chemistry and comprehensive metabolic profile including ALT, AST, Alk Phos and total bilirubin will be assessed during study visits. GVHD grading will be done per SOC. Treatment for GVHD will be captured.

All outlined study procedures are performed during clinic visits for routine post transplant care.

A serum level of isavuconazole will be performed once when patients have been on a steady oral dose of isavuconazole for 10-14 days.

In addition the subgroup of patients with GVHD grade ≥ 2 of the gastrointestinal system (GI) will have serum level of isavuconazole at diagnosis of GVHD and 2 weeks after starting treatment for GVHD.

Follow up will take place in the hospital if patients are hospitalized and at the BMT clinic during routine clinic visits when pts are outpatients.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Study day 1 [First day of dosing (FDD)] through week 14 post-HCT.

The following assessments will be performed twice per week on two non-consecutive days, preferably three days apart (e.g., Mondays and Thursdays) from study Day 1 through week 3, weekly from week 4-8, every 2 weeks from week 9-14.

A table of study procedures and assessments is provided in section 8.0.

The following will occur during the visit.

1. Review of medications performed by BMT pharmacists (through week 14 or discontinuation of prophylaxis)
2. Vital signs: body temperature, blood pressure, body weight, and pulse rate. Interim history and directed physical exam. The physical exam should focus on organs systems that are clinically relevant in the setting of invasive fungal infections.
3. Review of any adverse events. Only those events which are deemed to be at least possibly related to isavuconazole will be graded and attributed.
4. Blood tests
 - Hematology: complete blood count with differential and platelet count

- Serum chemistry: creatinine, blood urea nitrogen, AST, ALT, alkaline phosphatase, total bilirubin, sodium, potassium, chloride, calcium, magnesium, and albumin
5. If the patient is diagnosed with a fungal infection or a fungal infection is suspected, isavuconazole will be held and empiric treatment for fungal infection will be initiated per SOC. Work up for fungal infection will be performed per SOC.

The clinical work up for suspected fungal infections may include, but is not limited to, checking fungal markers in serum (galactomannan and BD glucan), CAT SCAN of the chest, CAT scans of the abdomen/pelvis, head or sinuses, bronchoscopy, or other procedure for tissue sampling depending on presenting signs and symptoms.

Follow up (week 15 or discontinuation through week 26)

The following assessments will be performed every 4 weeks during the follow up period:

1. Interim history
2. Review antifungal medications
3. Blood tests: CBC and comprehensive metabolic profile

11.0 TOXICITIES/SIDE EFFECTS

Study drug will be discontinued if clinically indicated for treatment emergent adverse events that are thought to be related to isavuconazole. However if another etiology is judged by the PI to be the likely cause of toxicity and an interval of no more than 14 days has lapsed the study drug can be resumed at original dose. If the same toxicity recurs the patient will be withdrawn from the study treatment.

- For any Grade III or IV toxicity according to NCI common terminology criteria of adverse events (CTCAE) version 4.0 which is not typically expected in the course of BMT and may be possibly related to study drug.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The primary endpoint is the rate of clinical failure by post- HCT week +14.

Clinical failure is defined as:

- 1) Systemic antifungal therapy for > 14 consecutive days for suspected fungal infection up to week 14. The >14 consecutive days must be completed by week 14 to meet the definition of clinical failure.
- 2) Breakthrough proven or probable fungal infection during the prophylaxis phase. The prophylaxis phase is defined as the period from the first dose of isavuconazole through 7 days after discontinuation (Definitions for proven or probable fungal infections are provided in Appendix 1).

- 3) Toxicity leading to permanent discontinuation of prophylaxis
- 4) Adverse event requiring discontinuation.

13.0 CRITERIA FOR REMOVAL FROM STUDY

In accordance with the Declaration of Helsinki, ICH Good Clinical Practice Guidelines, and the US FDA Regulations, a patient has the right to withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution. The Investigator also has the right to withdraw patients from the study (see below). Should a patient (or a patient's legally authorized representative) decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible.

A complete final evaluation will be made at the time of the patient's withdrawal with an explanation of why the patient is withdrawing, and an attempt should be made to perform a follow-up evaluation.

Patients may be removed from study if one or more of the following events occur:

- Significant noncompliance on the part of the patient
- Refusal of the patient to continue treatment or observations
- Unacceptable toxicity
- Decision by the Investigator

14.0 BIOSTATISTICS

Primary Objective:

This is a single center open label trial of isavuconazole for prevention of fungal infection in patients undergoing HCT for hematologic malignancies at MSK.

Patients who receive > 2 doses of isavuconazole are considered evaluable for the primary endpoint. The primary endpoint is the rate of clinical failure by post-HCT week +14. Clinical failure is defined in Section 12.0. Patients who die, or relapse while on prophylaxis, will be considered evaluable for the primary endpoint; clinical failure will be evaluated based on the time on study as long as the patient received more than two doses of isavuconazole. This endpoint definition aligns with a competing risk analysis.

On the basis of the prior multicenter, randomized prophylactic trial of voriconazole the rate of clinical failure for voriconazole is estimated at 40-50% (Wingard JR et al, 2010). We estimate the rate of clinical failure in our historical control to be 50%. Therefore, we will consider isavuconazole prophylaxis promising and worthy of future investigation if the clinical failure rate is 36% or less. Using these rates, a single-stage exact design will be implemented. A total of 85 evaluable patients will be included in the primary endpoint. If no more than 36 out of 85 patients have clinical failure, the intervention will be considered promising for further investigation. The type I and type II errors are both set at 0.10.

This is a single arm study of prophylaxis with a composite endpoint. There will be no interim analysis for this study. Isavuconazole is FDA approved for treatment of fungal infections. The safety and efficacy of isavuconazole has been assessed in a phase 3 study for treatment of fungal infections. In that randomized study isavuconazole demonstrated similar efficacy to voriconazole but better tolerability and safety profile than voriconazole.

We will accrue 100 subjects to ensure at least 85 evaluable patients. Patients will be evaluable if they have received > 2 doses of isavuconazole. Patients who receive ≤ 2 doses of isavuconazole will be considered non-evaluable and will be replaced. In the event that more than 85 of the 100 are evaluable for the primary endpoint, only the first 85 evaluable enrolled on study will be included in the evaluation of the primary endpoint. We anticipate accrual of approximately 4 patients per month and hence accrual should be completed in 24 months and follow up by 36 months.

Secondary Objectives:

1. Descriptive statistics will be used to assess serum levels of isavuconazole in patients with grade ≥ 2 acute graft versus host disease (GVHD) of the gastrointestinal tract.
2. Estimate the incidence of probable or proven breakthrough invasive fungal infections (IFIs) with isavuconazole prophylaxis at end of study (week 26) using cumulative incidence functions. Death in the absence of IFIs is considered a competing event for this analysis.
3. Describe reasons for discontinuation of prophylaxis of isavuconazole. The number and type of adverse events (AE) leading to discontinuation of isavuconazole will be described and the severity grade and relationship of the AE to isavuconazole will be reported.
4. Kaplan-Meier methods will be used to estimate overall survival at week 26.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

This is a single arm, open-label study. There is no randomization.

16.0 DATA MANAGEMENT ISSUES

This is a single institution study. All patients will be treated at Memorial Sloan Kettering Cancer Center. A research study assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization and coordinate the activities of the protocol study team. The data manager will also monitor laboratory compliance throughout the study. Laboratory data will be tabulated and summarized based on MSK normal ranges.

Data collected for this study will be entered into the MSK clinical research Database (CRDB).

SAEs will be reported According to section 17.2.

AEs will be documented in the patient's medical records **only if the event is considered at least possibly related to ISA**. Evidence of the relationship will be initially captured as SOC. In the event that event is reported as at least possibly related, the PI or Co-PI will review the patient's medical records and will grade attribute the relationship between the event and ISA on a separate document.

Any event that began before ISA therapy is initiated will be considered as medical history and will only be captured as an AE if the event worsens *after* ISA treatment is initiated and is deemed to be at least possible related to ISA. AEs will be recorded from ISA treatment initiation through 24 hours after the last dose.

At an accrual rate of approximately 4 patients per month we anticipate to reach accrual in 24 months. With an estimated follow up of 6 months we plan to complete the study in 36 months.

16.1 Quality Assurance

Registration reports will be generated by the RSA on a regular basis to monitor patient accruals and completeness of the registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Memorial Sloan Kettering Cancer Center (MSK) has established standard procedures for data safety monitoring of clinical research (see Data and Safety Monitoring Plans).

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) plans at MSK were approved by the National Cancer Institute (NCI) in September 2001. The plans address the new policies set forth by NCI in the document titled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: <http://cancertrials.nci.nih.gov/researchers/dsm/index.html>. The DSM Plans at MSK were established and are monitored by the Office of Clinical Research. The MSK Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: <http://mskweb2.mskcc.org/irb/index.htm>.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (i.e. NIH sponsored, in-house sponsored,

industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

Consent process: Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to MSK IRB guidelines.

Benefits: It is known that isavuconazole has activity against the fungal pathogens causing infections in HCT recipients. Isavuconazole has been effective for the treatment of aspergillosis and other rare molds in immunocompromised patients. Isavuconazole compared to voriconazole has less drug-drug interaction and lower frequency of adverse events including visual and central nervous system effects, skin eruptions and laboratory abnormalities

Protocol Amendments and Study Termination: All protocol amendments will be reviewed and approved by the Institutional Review Board of Memorial Hospital before implementation.

Incentives: No incentives will be offered to patient/subjects for participation in this study. Participation is voluntary.

Costs: isavuconazole will be provided by Astellas and will be free of charge to the patients.

Eligibility Exceptions: There will be no exceptions to the eligibility requirements for this protocol without the authorization of the Institutional Review Board of Memorial Hospital.

Adverse Reporting Requirements: AEs will be documented in the patient's medical records. The PI or Co-PI will attribute the relationship between the event and ISA.

Any event that began before ISA therapy is initiated will be considered as medical history and will only be captured as an AE if the event worsens *after* ISA treatment is initiated. AEs will be recorded from ISA treatment initiation through 1 day after the last dose.

Inclusion of Children in Research: Isavuconazole is not approved for children under 18 years of age. The protocol does not include children.

Inclusion of women and minorities: Memorial Sloan-Kettering Cancer Center has filed form HHS 441 (re: Civil Rights), form HHS 641 (handicapped Individuals), and form 639-A (re: Sex Discrimination). In selecting patients for study in the projects proposed in this protocol, we have taken due notice of NIH/ADAMHA policies concerning inclusion of women and minorities in clinical research populations. We expect that the study population will be fully representative of the range of patients seen at Memorial Hospital without exclusion as to age, gender, or ethnic background.

Alternatives to the Planned Study: Alternative treatment options include receiving standard antifungal prophylaxis with voriconazole or participation in other investigational studies. If relevant, other investigational options will also be outlined.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patient's names or any other personally identifying information will not be used

in reports or publications resulting from this study. The Food and Drug Administration or other authorized agencies (e.g., qualified monitors from MSKCC or the NCI etc.), and appropriate personnel may review patient records as required.

17.1 Privacy

It is the responsibility of the Research Staff to ensure that protocol subjects received the Center's Notice of Protocol Practices. If the subject has not received one, MSK personnel must provide a Notice of Privacy Practices and obtain acknowledgment before the subject participates in the study.

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required after the participant consents to the study and is fully registered. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSK)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
 - A explanation of how the AE was handled
 - A description of the subject's condition
 - Indication if the subject remains on the study
 - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

17.2.1

All serious adverse events will be reported to Astellas at: safety-us@us.astellas.com.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)

4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

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20.0 APPENDICES

1. Appendix 1. MSG/EORTC definitions of possible, probable, and proven invasive fungal infections. (DePaw B et al. 2008)
2. Appendix 2. A list of CYP3A4 inducers. (Vfend {package insert} Pfizer, New York, NY, <http://labeling.pfizer.com/ShowLabeling.aspx?id=618>)